

PB83-129981

The Acute Effects of 0.2 ppm Ozone in
Patients with Chronic Obstructive
Pulmonary Disease

(U.S.) Health Effects Research Lab.
Research Triangle Park, NC

5 Jan 82



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1. REPORT NO. EPA-600/J-81-330		2. JOURNAL ARTICLE		3. PB83-129981	
4. TITLE AND SUBTITLE The Acute Effects of 0.2 ppm Ozone in Patients with Chronic Obstructive Pulmonary Disease				5. REPORT DATE 1982	
				6. PERFORMING ORGANIZATION CODE	
7. AUTHOR(S) J.J. Solic, M.J. Hazucha, and P.A. Bromberg				8. PERFORMING ORGANIZATION REPORT NO.	
9. PERFORMING ORGANIZATION NAME AND ADDRESS Human Studies Division, HERL, US EPA, RTP, NC 27711 Center for Environ. Health and Med. Sci., School of Med., UNC, CH, NC				10. PROGRAM ELEMENT NO.	
				11. CONTRACT/GRANT NO.	
12. SPONSORING AGENCY NAME AND ADDRESS Office of Research and Development Health Effects Research Laboratory US Environmental Protection Agency Research Triangle Park, NC 27711				13. TYPE OF REPORT AND PERIOD COVERED	
				14. SPONSORING AGENCY CODE EPA-600/11	
15. SUPPLEMENTARY NOTES REF: American Rev. Resp. Disease, 125(6):664-669, 1982					
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17. KEY WORDS AND DOCUMENT ANALYSIS					
a. DESCRIPTORS		b. IDENTIFIERS/OPEN ENDED TERMS		c. COSATI Field/Group	
REPRODUCED BY NATIONAL TECHNICAL INFORMATION SERVICE U.S. DEPARTMENT OF COMMERCE SPRINGFIELD, VA 22161					
18. DISTRIBUTION STATEMENT Release to Public		19. SECURITY CLASS (This Report) Unclassified		21. NO. OF PAGES 9	
		20. SECURITY CLASS (This page) Unclassified		22. PRICE	

The Acute Effects of 0.2 ppm Ozone in Patients with Chronic Obstructive Pulmonary Disease¹⁻³

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Introduction

Ozone (O_3), the major oxidant in photochemical smog, is known to cause respiratory symptoms when inhaled in the concentrations sometimes found in the atmosphere of major urban areas of the United States. The National Ambient Air Quality Standards for ozone and other photochemical oxidants have been intended to assure an adequate margin of safety to protect the public health. In interpreting the Clean Air Act, the Environmental Protection Agency has stated that "in protecting public health, the population segments of primary concern are the most susceptible groups, in whom exposure to ozone or other pollutants is most likely to promote impairment of health." Although the present ozone standard (0.12 ppm, 1 h average) has been arbitrarily defined to protect such "high risk" groups, it was derived primarily from animal studies, epidemiologic data, and exposure studies in normal human volunteers (1). Limited epidemiologic data (2-8) would suggest the patients with chronic obstructive pulmonary disease (COPD) might be more sensitive to the effects of oxidant pollutant exposure and, therefore, constitute a "high risk" subgroup that represents a significant proportion ($\approx 4\%$) of our population (9).

To date, there have been no well-controlled studies of the response of patients with COPD to ozone. Several studies performed in the early 1960s measured the acute effects of exposing patients with COPD, living in an area with high ambient concentrations of oxidants, to filtered air in a chamber. These studies suggested that atmospheric oxidants may have had a deleterious effect on the baseline pulmonary function of these patients (10-12). A number of epidemiologic studies have also suggested an association between oxidant pollutant exposure and aggravation of pre-existing respiratory disease

SUMMARY Epidemiologic data suggest that patients with chronic obstructive pulmonary disease (COPD) might be more sensitive than normal persons to the respiratory effects of oxidant pollutant exposure. Our study was designed to determine the response of patients with COPD to ozone. Thirteen white men with nonreversible airways obstruction (mean FEV₁/FVC, 58%), of whom 8 were current smokers, were randomly exposed for 2 h to air and to 0.2 ppm ozone on 2 consecutive days using a single-blind crossover design. During either exposure, subjects exercised for 7.5 min every 30 min. Measures of respiratory mechanics obtained pre-exposure and postexposure were not significantly affected by either exposure. Similarly, ventilation and gas exchange measured during exercise showed no differences either between exercise periods or exposure days. However, arterial O_2 saturation (SA_{O_2}), measured by ear oximetry during the final exercise period each day was lower (94.8%) at the end of O_3 exposure, than SA_{O_2} obtained at the end of air exposure (95.3%), the difference (0.48%) being significant ($p = 0.008$). Because normal subjects undergoing comparable exposures show a threshold for respiratory mechanical effects at about 0.3 ppm ozone, our data suggest that mild to moderate COPD is not associated with increased sensitivity to low ozone concentrations. However, our data do not rule out the possibility that the response of such subjects might be exaggerated at higher ozone concentrations. The consistent (in 11 of 13 subjects), though small, decrease in SA_{O_2} may indicate that indexes of ventilation/perfusion distribution might be more sensitive measures of ozone effect in this compromised patient group than are conventional respiratory mechanics measures.

AM REV RESPIR DIS 1982; 125:664-669

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(2-8). Several investigators have observed positive associations between oxidant exposures and a subsequent increase in hospital admissions (5, 6). Although these studies are suggestive, definitive conclusions cannot be derived from any of them. The present study represents an initial approach to defining the acute response of patients with COPD to a low concentration of ozone.

Methods

Subject selection. Approval was obtained from the Committee for the Protection of the Rights of Human Subjects, University of North Carolina School of Medicine, before beginning the experiment. The subjects were recruited from the patient population of the North Carolina Memorial Hospital. One of the investigators (JS) reviewed the pulmonary function data for all white men, 40 to 70 yr of age with COPD, who had been admitted to the hospital or had pulmonary function tests performed in the hospital's pulmonary laboratory during 1980. Selected patients were contacted and invited to be evaluated for the study. Those agreeing to participate underwent a screen-

ing examination that included a medical history, physical examination, biochemical profile, clinical blood count (with leukocyte differential), chest roentgenogram, resting arterial blood gas determinations, and a 12-lead electrocardiogram. Baseline pulmonary function tests performed included forced vital capacity (FVC) (preinhalation and postinhalation of 0.5 ml of 1% isotharine), vital capacity (VC), functional residual capacity (FRC), and airway resistance (Raw). The subjects also exercised for

(Received in original form September 18, 1981 and in revised form January 5, 1982)

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² Supported in part by Research Grant No. RR-46 from the General Clinical Research Center Branch of the Division of Research Resources, Public Health Service.

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a 10-min period on a treadmill at a speed calculated to increase their minute ventilation ($\dot{V}_E$) to 20 to 30 L/min. During this period, 12-lead electrocardiographic tracings were recorded to measure heart rate and to determine if any significant underlying cardiovascular disease was detectable. Patients who gave informed consent and were able to perform the required maneuvers (treadmill walking, spirometry, and body plethysmography) were included in the study only if they fulfilled the following criteria: (1) No significant hypertension or atherosclerotic cardiovascular disease by history, physical examination, or exercise testing (i.e., no history of congestive heart failure, angina, claudication, transient ischemic attacks, or myocardial infarction; absence of multifocal premature ventricular contractions or ST-segment depression during exercise). (2) Pulmonary function tests demonstrating a forced expiratory volume in one second (FEV_1) $\geq 40\%$ of predicted, a FEV_1/FVC of 40 to 70%; no decrease in RV or FRC, no hypercapnia at rest, nonreversible airway obstruction after inhalation of 0.5 ml of 1% isoetharine in 2.5 ml saline nebulized with a DeVilbiss No. 561 nebulizer; a reversibility defined as a $\geq 15\%$ change in 2 or more of the following: FVC, FEV_1 , or maximal mid-expiratory flow rate ($FEF_{25-75\%}$). The study population was intended to represent a clinical spectrum from mild to moderate COPD, closely corresponding to the Categories I and II defined by Gaensler and Wright (13). Patients with severe respiratory impairment were excluded from the study because it was felt that they were less likely to be outdoors during episodes of air pollution and therefore at less risk than patients with milder disease who would continue to be active during these periods. All of our subjects were residents of North Carolina and had had no significant exposure to ambient pollutants (14).

Environmental control system. All exposures were performed at the Environmental Protection Agency's CLEANS facility on the campus of the University of North Carolina in Chapel Hill. Details of the facility have been described previously (15, 16). Briefly, chamber air flow, pollutant burden, temperature, relative humidity, light intensity, and chamber pressure were carefully controlled and monitored by appropriate sensors linked to an independent exposure control computer system (PDP 11/40). All instruments were maintained and calibrated weekly by the Operations and Maintenance Contractor, Rockwell International.

One or 2 subjects at a time were studied in the controlled environment of $22^\circ \pm 1^\circ$ C, 40% relative humidity, and light intensity of 50-foot candles. Ozone was produced on site by ultraviolet irradiation of air and monitored continuously by at least 2 chemiluminescent analyzers (Bendix, 8002, and DASIBI, 1003-AH). The total airborne par-

ticle mass was routinely $< 3 \mu\text{g}/\text{m}^3$ with approximately 10^4 particles/ m^3 .

Exposure protocol. All studies were conducted during a 2.5 month period from late January to early April. The protocol consisted of 2 exposure days, 1 to O_3 at 0.2 ± 0.01 ppm and 1 to purified air with an initial odor sham (O_3 at 0.1 ppm for 5 min followed by purified air). The study was of a two-period crossover design, so that each subject was tested under both exposure conditions and served as his own control. Subjects were randomly assigned to receive either air or O_3 on the first exposure day. Seven subjects received O_3 first and 6 received air first. Most subjects stayed in the Clinical Research Unit of the North Carolina Memorial Hospital for the 2-day experiment. They were admitted on the afternoon prior to the first exposure day. At that time, a brief physical examination was performed and the subjects participated in a training session at the CLEANS facility that included spirometry, body plethysmography, and ear oximetry.

Subjects who were taking oral medications were allowed to continue them throughout the study. However, subjects were required to discontinue the use of inhaled bronchodilators on the mornings of both exposure days and during the actual exposure period. Current smokers were asked to refrain from smoking after midnight prior to each exposure day. However, if they could not stop smoking during that period of time, each subject was asked to keep a record of his smoking pattern after midnight and to attempt to duplicate this pattern on the following night. Venous COHb concentrations were measured on arrival in the laboratory and were essentially the same on both days for each subject. No smoking was permitted starting 1 h before baseline measurements and during the actual exposure period.

All but 1 of the subjects were studied on 2 consecutive days, with each session beginning at approximately 8:00 A.M. One hour before beginning the exposure, the subjects performed a set of baseline pulmonary function tests in the FRC, Raw, FVC sequence while breathing purified air and completed a symptom questionnaire. At the appropriate time, each subject reentered the chamber for a 2-h exposure. Each half hour, subjects exercised by walking for 7.5 min on a treadmill. The speed and elevation were individually set to increase each subject's $\dot{V}_E$ to 20 to 30 L/min and his $\dot{V}_{O_2}$ to approximately 1 L/min. This amount of exercise was chosen to simulate the amount of work each subject would perform while walking outdoors during an air pollution episode. For monitoring purposes, several FVC maneuvers were performed by each subject at 1 h of exposure. Postexposure plethysmography followed by spirometry was performed while the subject was still in the chamber, breathing the atmosphere for

that exposure day. Upon completion of these tests, the subjects left the chamber and completed another symptom questionnaire.

Measurement techniques. All pulmonary function data were acquired on-line on a PDP 11/40 computer. Symptom questionnaire data were subsequently merged with the other data for analysis. The SaO_2 off-line data were analyzed independently. The following tests were used in the assessment of response.

Body plethysmography: FRC, Raw, and the corresponding thoracic gas volume were measured at 90 bpm in a body plethysmograph (CPI model-2000; Cardio-Pulmonary Instruments, Houston, TX) using the method of DuBois and coworkers (17, 18). For each test condition, trials were repeated until at least 3 maneuvers, 2 of which were technically acceptable and within 10% of each other, were obtained. These 2 trials were averaged and used for statistical analysis.

Spirometry: The FVC maneuver was performed on a dryseal spirometer (Model 220; Ohio Instruments, Madison, WI). The specifications for the FVC analysis exceeded criteria set forth by the American Thoracic Society (19). Three or more maneuvers were performed until at least 2 technically acceptable FVC maneuvers within 10% of each other were obtained. Only these 2 spirometers were averaged and statistically analyzed. The following measurements were derived: FVC, FEV_1 , maximal flows with 50 and 25% of FVC remaining ($\dot{V}_{\text{max}50\%}$ and $\dot{V}_{\text{max}25\%}$), $FEF_{25-75\%}$, and flow rate between 200 and 1,200 ml of FVC ($FEF_{200-1,200}$).

Cardiopulmonary parameters: During the sixth and seventh minute of each exercise period, the subject was asked to breathe through a Fleisch No. 3 pneumotachometer. The following variables were recorded on-line: $\dot{V}_T$, respiratory rate (f), $\dot{V}_E$, oxygen consumption ($\dot{V}_{O_2}$) and respiratory exchange ratio (RER) carbon dioxide production ($\dot{V}_{CO_2}$). Gases were continuously sampled at the mouth and analyzed for concentrations of O_2 and CO_2 by a mass spectrometer (Model MGA 1100; Perkins-Elmer Medical Instruments, Pomona, CA). These data were used to quantify exercise performance on each exposure day.

Ear oximetry: After arterialization of the ear, each subject wore an ear oximeter sensor (Model 47201A; Hewlett-Packard, Waltham, MA) during the last exercise period on each day. The analog signal was recorded on an X-Y recorder (Model 7047; Hewlett-Packard) and simultaneously on a digital multimeter (Model 3400; Data Precision), interfaced with a digital panel printer (Model DPP-7; Datal, programmed to average signal at 30-s intervals. From these averages, an overall mean saturation for the whole 7.5-min period was calculated.

Symptom questionnaire: a simple symptom questionnaire designed to elicit symptoms

- associated with pollutant exposure was administered by one of the physicians before and after each exposure period.

Statistics. Multivariate analysis of variance was used to analyze spirometric, plethysmographic, and exercise data. For each parameter, the main hypothesis tested was that the change from preexposure to post-exposure was the same during the air and ozone days. Each parameter was also tested for carry-over effects of exposure (ozone and air). Symptom questionnaire results were analyzed using the nonparametric Wilcoxon's rank-sum statistic. A nonparametric approach was chosen to free the analysis of certain distributional assumptions that might be questionable because of the small sample size. These data were also checked for carry-over and exposure effects. The SAO_2 data were analyzed using the *t* test for paired data. Because, from all of the variables measured, only 4 (FEV_1 , Raw , $\dot{V}_E$, and SAO_2) were targeted for evaluation of O_3 effects, a more stringent *p* value of 0.0125 (0.05 divided by 4) was used to reject the individual null hypotheses.

Results

Individual physical characteristics, symptoms, smoking history, medications,

and chest roentgenographic findings of the patients participating in the study are given in table 1. All of the patients had been previously diagnosed as having COPD by other physicians. Results of our screening tests supported this diagnosis. The patients were all white men 43 to 69 yr of age with a mean age of 56. All but one had been heavy smokers in the past and the majority (8 of 13) were still smoking at the time of the study. All of the subjects had chronic symptoms (present for at least 1 yr) that ranged from mild exertional dyspnea to dyspnea at rest, cough, wheezing, and daily sputum production. Chest roentgenogram changes associated with COPD (bullous changes and/or hyperinflation) were present in all but 2 subjects. Six of the patients were taking medications commonly used in the treatment of patients with respiratory disease.

Baseline pulmonary function and blood gas measurements (table 2) further supported the diagnosis of COPD. Although the mean FVC (3.96 L) was within the mean predicted range, mean

FEV_1 (2.28 L) and mean FEV_1/FVC (57.5%) were both decreased, as expected from the subject selection criteria (20). In addition, mean FRC for the group was increased (123.2% of predicted) with significant elevations of FRC in 9 of 13 subjects (21). Resting arterial blood gases demonstrated hypoxemia (mean PO_2 of 69.6 mm Hg) without CO_2 retention (mean PCO_2 of 37.1 mm Hg).

The symptom questionnaire contained 2 sets of questions that were intermixed: a control set (i.e., eye irritation, anxiety, etc.) and a set known to be associated with O_3 exposure (i.e., substernal discomfort, inspiratory difficulty, etc.). Scores were calculated for all symptoms combined and for the subset of ozone-related symptoms. There was no significant difference between air and ozone days for either the total symptom score or the O_3 related subset. There was no correlation between individual decrements in pulmonary function tests and either symptom score.

Selected pulmonary function data for air and ozone days are shown in ta-

TABLE 1
PATIENT CHARACTERISTICS

Patient No.	Age (yr)	Height (cm)	Weight (kg)	Medications	Smoking History		Chronic Symptoms	Chest Roentgenogram
					Past	Present		
2	43	188	106	Theophylline	60 py	2-3 ppd	Cough, sputum, wheezing, exertional dyspnea	Increased interstitial markings
3	45	174	72	None	40 py	1 ppd	Cough, sputum, exertional dyspnea	Bullous changes; increased interstitial markings
5	57	183	82	Theophylline Metaproterenol Cromolyn	70 py	1/2 ppd	Cough, wheezing, exertional dyspnea	Bullous changes; increased interstitial markings; hyperinflation
6	69	172	55	Theophylline Metaproterenol Cromolyn	None	None	Cough, sputum, exertional dyspnea	Hyperinflation
7	54	180	78	Theophylline	80 py	10 cig/d	Cough, wheezing, exertional dyspnea	Bullous changes; increased interstitial markings
8	50	179	81	None	35 py	None	Exertional dyspnea	Apical scarring; pleural thickening
9	45	173	78	Haloperidol	80 py	1 ppd	Cough, sputum, exertional dyspnea	Increased interstitial markings; hyperinflation
11	59	172	68	None	60 py	8 cig/d	Cough, sputum, wheezing, exertional dyspnea	Bullous changes; hyperinflation
12	60	178	62	None	40 py	0.5 ppd	Cough, wheezing, exertional dyspnea	Bullous changes; hyperinflation
13	58	175	78	Theophylline Metaproterenol	100 py	1 ppd	Cough, wheezing, exertional dyspnea	Increased interstitial markings; hyperinflation
14	58	180	86	None	50 py	None	Cough, wheezing, exertional dyspnea	Bullous changes; hyperinflation
15	63	175	100	Intermittent antibiotics	80 py	None	Cough, sputum, exertional dyspnea	Increased interstitial markings; hyperinflation
17	63	169	60	None	50 py	None	Exertional dyspnea	Hyperinflation
Mean	56	177	77					

Definition of abbreviations: py = pack years (1 pack year represents 1 pack a day for 1 year); ppd = pack per day; cig/d = cigars per day.

TABLE 2
SELECTED BASELINE PARAMETERS*

Patient No.	FVC	FEV ₁	FEV ₁ /FVC (%)	FRC	pH	Po ₂	Pco ₂
2	4.6 (87) [†]	2.2 (52)	48	5.0 (114)	7.41	70	38
3	2.9 (66)	1.7 (49)	57	3.5 (97)	7.40	72	40
5	3.4 (72)	1.8 (61)	53	4.9 (119)	7.30	62	38
6	3.8 (97)	2.1 (72)	55	3.8 (105)	7.42	70	32
7	3.1 (67)	1.5 (43)	48	5.2 (133)	7.41	62	32
8	4.3 (93)	3.0 (83)	70	3.4 (87)	7.39	77	35
9	4.9 (113)	3.1 (88)	63	4.8 (133)	7.41	60	36
11	4.6 (115)	2.1 (68)	46	5.8 (165)	7.42	62	34
12	3.9 (89)	2.0 (61)	51	6.2 (159)	7.42	70	38
13	2.5 (53)	1.7 (52)	68	5.3 (143)	7.41	73	40
14	5.0 (109)	3.2 (91)	64	4.9 (123)	7.41	81	40
15	3.7 (88)	2.3 (74)	62	3.5 (95)	7.40	67	40
17	4.8 (123)	3.0 (100)	63	4.5 (129)	7.40	79	39
Mean	3.96 (90.5)	2.28 (68.8)	57.5	4.68 (123.2)	7.41	69.6	37.1
SE	0.2	0.2	2.3	0.3	0.0	2.0	0.9

* Predicted values for FVC and FEV₁ from Kory and coworkers (20); for FRC, from Bates and associates (21). Volumes in liters (LTPS); Blood gas measures in mmHg.

[†] Values in parentheses represent percent of predicted.

ble 3. There was no significant difference between the effect of the air exposure versus the ozone exposure in any of the parameters tested. Spirometric data showed no change in mean FVC or in mean FEF_{200-1,200} attributable to ozone exposure. Although the remaining mean forced expiratory flow rates were somewhat reduced after ozone exposure, none of these changes was statistically significant. Despite increases in mean Raw and SRaw after O₃ exposure (14 and 11%, respectively), none of the changes in plethysmographic data achieved significance either. Similarly, there was no significant difference between the effects of air and ozone exposure when comparing current smokers (n=8) with ex-smokers and nonsmokers (n=5). The 9

patients who demonstrated a greater degree of obstruction (FEV₁ < 2.3-L) were not significantly different from the rest of the patients in any of the parameters tested. Individual values for FEV₁ and Raw are shown in figures 1 and 2.

Analysis of cardiopulmonary parameters from the exercise periods on the air and ozone days showed that the subjects' performances on both days were practically identical. The following are mean values obtained on air and ozone days (air/O₃): $\dot{V}_{O_2}$ (1,002/1,002 ml/min); RER (0.88/0.88); $\dot{V}_T$ (1,326/1,374 ml); f (21/20 breaths/min); $\dot{V}_E$ (27.8/27.5 L/min); and heart rate (81/84 beats/min). There was no significant difference in any of these parameters between air and ozone days

or between individual exercise periods on each day.

The only parameter that showed a significant decrement during ozone exposure as compared with air exposure was SaO₂ (table 4). Mean SaO₂ after exposure to air was 95.3%, whereas mean SaO₂ on the day after ozone exposure decreased to 94.8% (p = 0.008). Practically all of the subjects (11 of 13) demonstrated a lower SaO₂ on the ozone day. Only 1 subject had a higher SaO₂ and 1 subject remained unchanged.

Discussion

The purpose of this study was to explore the sensitivity of patients with COPD to short-term exposure to low concentrations of ozone. It has been demonstrated in the past that ozone causes respiratory symptoms and pulmonary function decrements in resting normal subjects at a concentration of 0.5 to 0.6 ppm and at concentrations as low as 0.25 to 0.3 ppm with mild exercise (22-34). If patients with COPD are especially sensitive to the effects of ozone, we would expect to see enhancement of symptoms and greater pulmonary function decrements at these and lower concentrations than in normal persons.²

Because there were no controlled exposure studies reporting the effects of O₃ in patients with COPD, we chose a concentration of ozone that we felt would be safe for all patients, yet might still induce some response if, in fact, patients with COPD were especially sensitive to ozone. The concentration of 0.2 ppm appeared to be the most appropriate because no major adverse effects of ozone at this concentration have been reported in either normal subjects or asthmatics (35-37). Moreover, because this concentration of ozone is measured in many urban areas of the United States, many patients with COPD are frequently exposed to this amount of ozone.

It is well recognized that the group of patients included in the category of COPD is heterogeneous and difficult to characterize. It includes patients with a wide range of symptoms and ventilatory deficits. Earlier experiments using patients with COPD (10-12) have been criticized on the grounds that the patient population studied was too heterogeneous to arrive at any firm conclusions. We took great care in the selection of our patient population in order to keep the

TABLE 3
SELECTED PULMONARY FUNCTION DATA FOR AIR AND O₃ DAYS*

Test	Air		Ozone		pt
	Pre	Post	Pre	Post	
FVC, L, BTPS	3.86 ± 0.24	3.86 ± 0.28	3.86 ± 0.22	3.87 ± 0.23	0.827
FEV ₁ , L, BTPS	2.22 ± 0.16	2.23 ± 0.18	2.24 ± 0.16	2.18 ± 0.17	0.205
FEV ₁ /FVC, %	57.60 ± 1.80	58.80 ± 2.10	57.80 ± 2.20	55.80 ± 2.10	0.604
FEF ₂₅₋₇₅ %, L/s	1.09 ± 0.12	1.10 ± 0.15	1.12 ± 0.15	0.99 ± 0.13	0.084
FEF _{200-1,200} %, L/s	3.66 ± 0.48	3.59 ± 0.53	3.68 ± 0.47	3.63 ± 0.53	0.852
$\dot{V}_{max_{50\%}}$, L/s	1.52 ± 0.19	1.50 ± 0.23	1.49 ± 0.21	1.32 ± 0.19	0.149
$\dot{V}_{max_{75\%}}$, L/s	0.38 ± 0.04	0.40 ± 0.04	0.42 ± 0.05	0.38 ± 0.04	0.081
FRC, L, BTPS	4.66 ± 0.28	4.66 ± 0.25	4.65 ± 0.24	4.61 ± 0.23	0.670
Raw, cm H ₂ O/L/s	1.87 ± 0.30	1.95 ± 0.29	1.84 ± 0.26	2.10 ± 0.26	0.646
SRaw, cm H ₂ O × s	10.36 ± 1.96	10.51 ± 1.70	9.99 ± 1.53	11.06 ± 1.61	0.309

Definition of abbreviations: FVC = forced vital capacity; FEV₁ = forced expiratory volume in one second; FEF₂₅₋₇₅ = forced expiratory flow during the middle half of the FVC; $\dot{V}_{max_{50\%}}$ = maximal flow after exhalation of 50% of FVC; $\dot{V}_{max_{75\%}}$ = maximal flow after exhalation of 75% of FVC; FRC = functional residual capacity; Raw = airway resistance; SRaw = specific airway resistance.

* Values represent mean ± SE (n = 13).

[†] Significance levels (p values) between air and ozone groups.

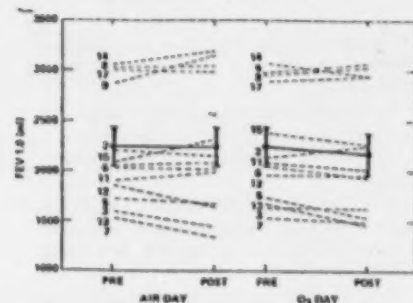


Fig. 1. Individual and group mean $\pm$ SEM for FEV₁ values preexposure and postexposure to air and ozone.

group as homogeneous as possible. Only white men with mild to moderate obstructive disease were included in the study. We felt that this subgroup would be most representative of the persons with COPD in urban areas of the United States who would be exposed to significant concentrations of ambient pollution. Patients with this degree of impairment are likely to be gainfully employed and, therefore, out of doors on days when the ambient concentration of ozone may be elevated. In contrast, most patients with severe obstructive disease might be more likely to be disabled and remain indoors during similar episodes. Of our group, most were still working and only 3 had retired for reasons attributable to COPD. Furthermore, the exercise protocol chosen for this experiment attempted to simulate the conditions that would be experienced by this group of

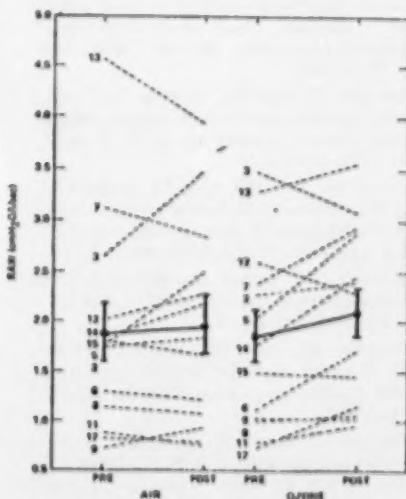


Fig. 2. Individual and group mean $\pm$ SEM for Raw values preexposure and postexposure to air and ozone.

Subject No.	Post-air	Post- O_3	Differential
2	93.3	93.0	-0.3
3	95.8	96.3	+0.5
5	95.9	95.3	-0.6
6	97.5	96.4	-1.1
7	96.3	95.8	-0.5
8	94.8	94.7	-0.1
9	94.9	94.3	-0.6
11	94.6	94.6	0
12	95.3	95.2	-0.1
13	95.0	93.8	-1.2
14	96.9	96.5	-0.4
15	92.7	91.9	-0.8
17	95.9	94.9	-1.0
Mean $\pm$ SE	95.3 $\pm$ 0.4	94.8 $\pm$ 0.4	-0.48 $\pm$ 0.14 p = 0.008

patients during a typical working day (short walks at a normal walking pace). Many patients with moderate COPD cannot sustain degrees of ventilation much higher than those required in our study (20 to 30 L/min) for any significant length of time.

A complicating factor in the selection of a homogeneous group was the smoking habits of the patients. The overwhelming majority of persons who develop COPD have smoked for many years prior to the development of symptoms or pulmonary function decrements. Thus, it would have been very difficult to exclude current or ex-smokers from our study. We attempted to control the effects of smoking as much as possible by prohibiting smoking during the experimental periods and by asking those patients who could not abstain to reproduce their smoking patterns on the nights prior to air and ozone exposure. We suspect that smokers with COPD would continue to smoke during episodes of elevated ambient pollution. Therefore, by allowing subjects to continue smoking, no potential change in their pulmonary function was introduced by reducing the effects of chronic cigarette smoke.

In our study of patients with COPD, we were unable to demonstrate any statistically significant effect of a 2-h exposure to 0.2 ppm ozone on respiratory mechanical function or on symptoms. Because none of the patients in our study were regularly exposed to elevated concentrations of ambient pollutants (ambient peak O_3 concentration < 0.08 ppm), adaptation and cross tolerance induced by such exposure (38-40) could not be responsible for suppressing their response to ozone. Another factor that can alter response to

ozone is minute ventilation during the exposure. Many studies of normal volunteers have documented that exercise amplifies the effects of any given concentration of ozone on respiratory symptoms and pulmonary function (29-32). Because the amount of exercise and total ventilation were comparable on both air and ozone days in our study, any lack of response cannot be attributed to differences in ventilation on each of the exposure days. The smoking habits of patients with COPD constitute another potential determinant of ozone response. There is some clinical data to suggest that at low concentrations of ozone, smokers demonstrate less decrement in pulmonary function measurements than nonsmokers (24, 34). Because 8 of our 13 subjects were current smokers, our observed lack of mean response to ozone might be attributable to this factor.

The decrements in SaO_2 seen after ozone exposure are intriguing. Although the measured changes are small and not likely to be clinically significant, they were observed in almost all of the subjects in the absence of any alteration in f , V_T , $\dot{\text{V}}_E$, $\dot{\text{V}}\text{O}_2$, or RER. Several possible mechanisms involving distribution of ventilation can be postulated for this observation. Because patients with COPD ventilate the relatively healthier areas of their lungs more efficiently than the diseased areas, more ozone may reach the lung regions served by these relatively normal airways. Consequently, if ozone exerted its effects directly, these airways and/or the subtended parenchyma could be more adversely affected by ozone than the diseased ones. In turn, this could lead to increased $\dot{\text{V}}/\dot{\text{Q}}$ mismatch, increased V_D/V_T , and a decrease in SaO_2 . Al-

though the clinical significance of this observation is not clear from our study nor can we determine underlying pathophysiologic mechanisms, the consistency and low variance of these changes in Sao_2 may warrant further investigation of this phenomenon.

In terms of the initial objective of this study, we demonstrated that at 0.2 ppm ozone, patients with COPD do not appear to be especially sensitive to the effects of ozone as measured by stated pulmonary function measurements. One must not extrapolate this lack of response to 0.2 ppm to higher concentrations of ozone, even considering the fact that because of their ventilatory limitations such patients may not be exposed to as high an "effective" concentration as are healthy persons. Furthermore, we must remember that significant decrement in pulmonary function in these patients will have a more deleterious effect than an equivalent change in a healthy person.

Acknowledgment

The writers thank Dr. William McDonnell, Dr. George Goldstein, Ms. Jean Litton, Ms. Martha Guttu, Mr. Dennis House, Ms. Paulette DeWitt, and Ms. Jo Nichols for their assistance during this experiment.

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